REMARKS

Amended claims 1, 3, 5, 19, 21 and 22 are submitted herewith. Limitations recited in claims 2 and 20 are incorporated into claims 1 and 19 as amended, and claims 2 and 20 are canceled herewith. Claim 19 has been amended to depend from claim 1. Claims 1, 3-5, 6-19, 21-44 remain pending with claims 6-18 and 24-44 withdrawn from consideration.

Support for amendment of claim 1 by insertion of the term "isolated" is found in the application as filed, for example at page 28, lines 1-5. Support for amendment of claim 1 by insertion of the term "wherein the active agent is selected from the group consisting of: an immunoglobulin (Ig) molecule and an Fc fragment of an immunoglobulin molecule" is found in the application as filed, for example at page 4, lines 11-13. Support for amendment of claim 1 by insertion of the term "wherein the target recognition segment (a) is covalently attached to the second segment (b)" is found in the application as filed, for example at page 8, lines 1-2; and page 11, line 32-page 12, line 5. Support for amendment of claim 1 by insertion of the term "in the form of a dimer" is found in the application as filed, for example at page 27, line 46-page 28, line 2.

Rejections under 35 U.S.C. 102

Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 02/08287.

Claim 1, as amended, is directed to an isolated polypeptide conjugate comprising:

(a) a target recognition segment comprising a Natural Killer cell receptor (NCR) or a fragment thereof, wherein the NCR is selected from the group consisting of: NKp30 or a functional fragment thereof that binds to a target tumor cell; and

(b) a second segment comprising an active agent capable of exerting a cytotoxic effect on the target cell, wherein the active agent is selected from the group consisting of: an immunoglobulin (Ig) molecule and an Fc fragment of an immunoglobulin molecule;

and wherein the target recognition segment (a) is covalently attached to the second segment (b); and wherein the conjugate is in the form of a dimer.

WO 02/08287 does not disclose a polypeptide conjugate of NKp30 and Ig or the Fc fragment of Ig in the form of a dimer, as claimed in amended claim 1. Furthermore, WO 02/08287 does not disclose a polypeptide conjugate comprising an immunoglobulin *molecule* and NKp30, as disclosed and claimed in the subject application.

Accordingly, WO 02/08287 does not teach and cannot anticipate the conjugate recited in claim 1 as amended.

Withdrawal of the rejection under 35 U.S.C. 102(a) is respectfully requested.

Claims 1-2 are also rejected under 35 U.S.C. 102(b) as being anticipated by Pende et al. According to the Office Action, Pende et al teach that addition of a full length antibody that cross-links NKp30, induces NK cytolytic activity (p. 1509, 2nd column, 3rd paragraph).

Pende et al. teaches the interaction between an antigen, in this case, NKp30 and an antibody that recognizes the antigen. The interaction between an antibody and its antigen can be disrupted by high salt concentrations, extremes of pH, detergents, and sometimes by competition with high concentrations of the pure epitope itself. The binding is therefore a reversible noncovalent interaction. In contrast, a conjugate involves the covalent linking of two molecules.

Pende et al clearly teaches an antibody/antigen interation and not a conjugate of NKp30 and an immunoglobulin or its Fc fragment. Claim 1 as amended is in fact directed to such a conjugate and is further distinguished over Pende et al in that the conjugate is *isolated*, the segment comprising NKp30 of fragment thereof is *covalently attached* to the segment comprising Ig or the Fc fragment of Ig, and moreover the conjugate is in the form of a *dimer*. Accordingly, Pende et al does not anticipate claim 1 as amended.

Withdrawal of the rejection under 35 U.S.C. 102(b) is respectfully requested.

Rejections under 35 U.S.C. 103

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being obvious over Pende et al, in view of Mandelboim et al, Nature, February 2001, 409: 1055-1060 (hereinafter "Mandelboim et al").

According to the Office Action, from the teaching of Pende et al it is clear that the Fc portion of an immunoglobulin is required for cross-linking NK30 and its activation, upon binding of the Fc fragment to its receptor on target cells.

The Office Action further indicates that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to replace NKp46 in the NKp46-Fc conjugate taught by Mandelboim et al with another member of the NCR family, NKp30, for making an NKp30-Fc conjugate for lysis of target cancer cells, in view that the conjugate NKp46-Fc by itself, without addition of a separate antibody, recognizes target cells, and induces lysis of target cells by NK cells, as taught by Mandelboim et al, and further in view that NKp30, but not NKp46, is the main NK receptor that lyses tumor cells, as taught by Pende et al.

The Office Action further indicates that SEQ ID NO:4 or its functional fragment is obvious in view that SEQ ID NO:4 is composed of a leader peptide of CD5, a KpnI restriction site, NKp30 and an Fc region. According to the Office Action, it would have been obvious to replace the signal peptide taught by Pende et al with a leader peptide and a restriction site for making and expressing the conjugate and for facilitating its secretion.

Applicants respectfully submit that the combination of Pende et al and Mandelboim et al does not render obvious the conjugate of claim 1 as amended, or the conjugate having SEQ ID NO:4 as recited in claim 5.

Applicants respectfully traverse the assertion in the Office Action that Pende et al teaches that NKp30, but not NKp46 is the *main* NK receptor that lyses tumor cells. Pende

et al in fact teaches that: 1) NKp30 and NKp46 together have a complementary role in the induction of natural cytotoxicity of certain tumor targets; 2) NKp30 cooperates with NKp46 and NKp44 in induction of NK-mediated cytotoxicity of certain tumor targets, and 3) NKp30 mediated lysis of certain tumor target cells is largely NKp46/NKp44 independent. More specifically, Pende et al discloses that anti-NKp30 antibody inhibits NK-mediated cytotoxicity of the tumor cell line MEL15, but has insignificant effect on NK-mediated cytotoxicity of the tumor cell line M14 in contrast to the effect of an anti-NKp46 antibody, and further, that the combination of anti-NKp30 antibody and anti-NKp46 antibody is required for efficient blocking of NK-mediated cytotoxicity of the tumor cell lines SMMC and A549 (see p.1510, col. 1-p.1511, col. 1 and Figure 5). Furthermore, Pende et al discloses that antibodies against all of NKp30, NKp46 and NKp44 have additive effects in inhibiting NK-mediated cytotoxicity of the tumor cell lines FO-1 and A549 (see p. 1511, col 1 and Figure 6).

Therefore, Pende et al characterizes the role of NKp30 in tumor cell killing in a qualified manner: "NKp30 plays a central role in the killing of MEL15" (p. 1510, col.2); "Analysis of...other tumor target cells such as SMCC and A549...revealed a balanced contribution of NKp46 and NKp30 to the induction of cytotoxicity"; "NKp30 could exert an additive effect in the induction of NK-mediated cytotoxicity, not only with NKp46, but also with NKp44" (p. 1511, col. 1).

Applicants respectfully traverse the assertion in the Office Action that Mandelboim et al teaches that the conjugate NKp46-Fc by itself induces lysis of target cells by NK cells. Rather, Mandelboim et al teach that the conjugate NKp46-Ig (i.e. the extracellular domain of NKp46 fused to immunoglobulin Fc) *binds* to haemagglutinin (HA) of influenza virus (IV) and to haemagglutinin-neuraminidase (HN) of parainfluenza virus, and that in a subset of NK cells *recognition* by NKp46 is required to lyse cells expressing the corresponding viral glycoproteins (see Abstract). More specifically, Mandelboim et al teaches that 721.221 cells infected with Sendai virus (SV) show increased binding to NKp46-Ig as compared to non-infected cells, that the effect is specific for NKp46 (see p. 1055, col. 2), that the binding is dependent on the viral HN,

but that SV-infected 721.221 cells do not show an increased susceptibility to NK-mediated lysis by effector cells (see p. 1056, col.1). Mandelboim et al further teaches that 293T cells transfected with HN also show increased binding to NKp46-Ig, that the HN-transfected 292T cells are efficiently lysed by NK_GAL, an NK line derived from healthy donor peripheral blood lymphocytes, and that antibodies against NKp46-Ig or against HN inhibit the lysis (see p. 1056, col. 2). Notably, these lysis experiments do not involve the conjugate NKp46-Ig (see legend to Figure 1, b and c). Similarly, Mandelboim et al discloses that 1106mel cells infected with IV show enhanced binding to NKp46-Ig and increased lysis by NK GAL and by certain clones thereof, and that antibodies against NKp46-Ig or against HA inhibit the lysis (see p. 1056, col. 2-p. 1057, col. 1). Notably, these lysis experiments do not involve the conjugate NKp46-Ig (see legend to Figure 2, a-c). Finally, Mandelboim et al teaches that NKp46 directly interacts with the sialic acid binding site of HA (see p. 1058, col. 1-col. 2). Mandelboim et al concludes that NKp46 *binds* to target cells in two ways: first, through the interaction of NKp46-associated sialic acid with viral sialic acid receptors, and second, in a sialic acid –independent interaction with undefined cellular ligands (see p. 1058, col. 2).

In accordance with the above, Applicants assert that it would not have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to replace NKp46 in the NKp46-Fc conjugate of Mandelboim et al with NKp30, for making NKp30-Fc for lysis of target cancer cells, since Mandelboim et al provides no teaching or suggestion that the conjugate NKp46-Fc induces or mediates lysis of target cells by NK cells, and Pende et al provides no teaching or suggestion that NKp30 is the main NK receptor for lysis of tumor cell targets.

Further, and importantly, neither Mandelboim et al nor Pende et al teach or suggest that a conjugate comprising *any* NK molecule and an Ig molecule or Fc fragment thereof exhibits direct cytolytic activity on target tumor cells, as surprisingly disclosed in the subject application (see Examples 2 and 3). Rather, as detailed above, Pende et al shows only that endogenously expressed NKp30 must be exposed on fresh NK cells for those cells to be able to mediate cytotoxicity of certain target tumor cells. Mandelboim et al teaches that the conjugate NKp46-Ig binds to virally-infected cells or to cells

expressing viral glycoproteins, but provides no teaching that the conjugate mediates lysis of such cells or any other targets of NK cells.

Furthermore, neither Mandelboim et al nor Pende et al teach or suggest a polypeptide conjugate comprising NKp30 covalently attached to Ig or the Fc fragment of Ig, wherein the conjugate is in the form of a *dimer*.

Applicants further assert that it would not have been obvious to replace the signal peptide taught by Pende et al with a leader peptide and a restriction site for making and expressing the conjugate having the amino acid sequence of SEQ ID NO:4. The application discloses that SEQ ID NO:4 (also referred to in the application as NKp30-Ig) does not contain the complete NKp30 protein sequence but rather includes only the extracellular portion thereof (see page 27, lines 43-44 of the application as filed). Further, the application teaches that NKp30-Ig has activity in directly mediating lysis of cancer cells (Example 2), and in mediating tumor regression in experimental animals (Example 3).

In contrast, Pende et al teaches cloning of a DNA sequence encoding the complete deduced NKp30 protein molecule, including the extracellular, transmembrane and cytoplasmic portions. However, Pende et al does not teach or suggest an isolated polypeptide conjugate in which a segment comprising NKp30 or a fragment thereof is covalently attached to a segment comprising an Ig molecule or an Fc fragment of an Ig molecule, wherein the conjugate is in the form of a dimer, nor that such a conjugate could have direct cytolytic activity or target tumor cells, as surprisingly disclosed in the subject application.

For the above reasons, withdrawal of the rejection under 35 U.S.C. 103(a) is respectfully requested.

Claims 19-23 are further rejected under 35 U.S.C. 103(a) as being unpatentable over Pende et al, in view of Mandelboim et al, as applied to claims 1-5, and further in view of Sukhatme et al (US 6,797,488).

According to the Office Action, the recitation in claims 19-23 of the claimed conjugate, formulated as a pharmaceutical composition is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. The Office action further indicates that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the conjugate with a pharmaceutically acceptable carrier, as taught by Sukhatme et al, for its storage.

Claims 19 and 21-23 as amended are dependent on claim 1. In accordance with the above explanations, claim 1 as amended is novel and non-obvious over the prior art including Pende et al and Mandelboim et al. Since base claim 1 is novel and non-obvious over the prior art, so too are claims 19 and 21-23 dependent therefrom, and may properly incorporate known subject matter. Claim 20 has been canceled, rendering moot the rejection of claim 20.

Withdrawal of this rejection under 35 U.S.C. 103(a) is respectfully requested.

Rejections under 35 U.S.C. 112

Claims 1-5 and 19-23 are rejected under 35 U.S.C. 112, first paragraph, allegedly because the specification, while being enabling for a conjugate of NKp30 or a fragment thereof that binds to a target tumor cell and an immunoglobulin or its Fc fragment, does not reasonably provide enablement for a conjugate of NKp30 or a functional fragment thereof that binds to a "cellular ligand" expressed on the surface of a target tumor cell, and "a fragment of an immunoglobulin".

Claim 1 as amended is directed to a polypeptide conjugate of NKp30 or a fragment thereof that binds to a target tumor cell and an immunoglobulin or its Fc fragment, which according to the Office Action, is enabled by the specification.

Claims 1-5 and 19-23 are rejected under 35 U.S.C. 112, second paragraph since claims 1 and 19 recite the term "active fragment" and it is not clear what type of activity is referred to. The Office Action further states that claim 5 is indefinite because it is not clear what type of function is referred to.

Applicants respectfully submit that the specification teaches the meaning of the rejected terms, however, in the interest of advancing the prosecution of the application, claims 1 and 5 as amended do not recite the allegedly indefinite terms.

Withdrawal of the rejections under 35 U.S.C. 112, first and second paragraphs is respectfully requested.

It is respectfully submitted that the above-identified application is now in a condition for allowance and favorable reconsideration and prompt allowance of these claims are respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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